REMARKS

The Examiner in this application has changed since the Office Action of 9 August 2007. Applicants thank the new Examiner for his suggestions and present additional claims 21-47 for consideration. In addition, Applicants invite the Examiner contact Applicants' agent to discuss any items that will advance prosecution of the case or to provide background related to prior prosecution of the case.

By way of background Applicants' amendment filed December 19, 2006 listed claim 5 as canceled and claims 11 and 12 as pending, however, the Office Action dated August 9, 2007 inadvertently omitted claims 11 and 12 as pending. Following entry of this amendment claims 1-4, 6-12, and 14-15, and 21-47 will be pending. Claims 1-10 and 14-15 were previously rejected.

Support for new claims 21-46 can be found throughout the specification and originally filed claims. For example, paragraphs 0152, 0154, 0155, 0156, 0161, 0162, 0163, 0164, 0183, 0186, 0189, 0190, 0191, 0194, 0195, 0196, 0197, and 0198 of the published application (US PreGrant Publication No. 2002/0110861) describe the individual components of the systems as claimed in the newly presented claims. Paragraphs 0282 and 0283 of the published application provide specific, non-limiting examples of the regulation system that have been reduced to practice.

New claims 21-46 recite a regulation system comprising three hybrid peptides and at least one ligand. Furthermore, the system claimed in claims 21-46 requires the ability to activate transcription of two genes of interest, using the three hybrid peptides. The hybrid peptides are designed such that two of the hybrid peptides, *e.g.,* hybrid peptides "A" and "B" must come together to form a dimer. This dimerization process is aided by the presence of a ligand to which both "A" and "B" can bind. This "A-B" dimer then acts as a transcription factor that can "turn on" a first gene of interest. The third member of the regulation system can dimerize with only one of the first two hyrid peptides, *e.g.,* "B" and "C" can dimerize together. In other words, one of the three hybrid peptides, *i.e.,* "B," participates in the two dimers. Again, the dimerization between "B" and "C" is aided by the presence of a ligand. This "B-C" dimer then acts as a transcription factor for another gene of interest. The ligands that aid in the dimerization of A-B and B-C may or may not be identical to one another.

Paragraph 0152 describes this regulation system and paragraphs 0282 and 0283 of the published application exemplify this regulation system. Paragraph 0282 describes two dimers:

(A)/(B)
(1) GAL4DmEcR-CDEF/VP16MmRXR-LmUSP-EFchimera,

(C)/(B)
(2) LexACfEcR-CDEF/VP16MmRXR-LmUSP-EFchimera

Continuing the discussion above, the first dimer is between "A" and "B" and the second dimer is between "C" and "B." The underlined portion of each dimer is identical and represents the hybrid peptide that is shared between the two dimers, *i.e.*, hybrid peptide "B."

Paragraph 0283 describes two more dimers:

(A)/(B)
(1) GAL4CfEcR-DEF/VP16MmRXRα-EF,

(C)/(B)
(2) GAL4NcEcR-CDE/VP16MmRXRα-EF

Once again, the first dimer is between "A" and "B" and the second dimer is between "C" and "B." The underlined portion of each dimer is identical and represents the hybrid peptide that is shared between the two dimers, *i.e.*, hybrid peptide "B."

Accordingly, the new claims do not introduce new matter to the application.

Written Description under 35 U.S.C. § 112(1)

Claims 1-10 and 14-15 stand rejected under 35 U.S.C. § 112 first paragraph by the USPTO for failing to comply with the written description requirement. Specifically, the USPTO has stated that the claims are directed to multiple gene expression systems which are not adequately described in the specification.

The specification conveys written description support for the multiple gene expression systems claimed. For example, page 6, lines 12-14 of the application as originally filed states "Applicants' invention provides a multiple inducible gene regulation system that allows the simultaneous and quantitative regulation of two or more different genes....". Also, page 7, lines 6-7 states "An advantage of Applicants' invention is that it provides a means to regulate expression of two or more genes…". Further, page 28, lines 20-21 states: "In particular, Applicants describe herein a novel inducible gene expression system comprising at least two individually operable gene expression systems."

Further, it is not necessary for Applicants to have provided structures of more than two ligands and nuclear receptors that act independently of each other to fulfill the written description requirement. Applicants point out that the ligands and receptors of the Examples are not limited for use in just a dual system, but are also designated for use in modulation systems where more than two genes of interest are regulated, as the specification states (page 60, line 19) "for use in a multiple inducible gene expression system of the invention." In contrast to the case law and examples cited by the USPTO, additional ligands and receptors for use in multiple systems are not structures isolated from nature, but are based on the *rational modification of well characterized structures* which is taught in the specification. Applicants

point out that the Federal Circuit has made clear in *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006) that actual reduction to practice is not required for written description. However in addition to Applicants' description of actual reduction to practice of such a system: the structure and function of two working embodiments of an orthogonal, multiple inducible gene expression modulation system, Applicants' also provided significant written description to a skilled artisan for ligands and receptors for use in a multiple inducible gene expression system.

For example, page 40, line 3-6 states:

> "To develop a set of non-cross-interactive ("fully orthogonal") ligand/receptor pairs the lead structures for both ligand and receptor are maximally structurally diverse. For ecdysone-based receptors, two chemotypes are ideal for use as ligands: the natural ecdysteroids, such as, for example, 20-hydroxyecdysone, and the diacylhydrazines."

Also, page 41, lines 3-27 states:

> "Since a multiple gene regulation system requires discreet ligands that will not cross-react among themselves or with other receptors within the cell, but are specific for and induce only a specific receptor, several strategies are used to define the appropriate ligands for each multiple gene regulation system combination.
> Ligand complementation starts from a known highly active ligand and proceeds in one of three ways:
>
> 1) Stepwise change of individual pharmacophore (i.e., active site) element (PE) identity on the ligand, wherein a ligand pharmacophore is hypothesized, an element within the pharmacophore is dramatically altered and a mutant receptor library is queried for a complementary alteration. Once a successful mutant/ligand combination is identified, a protein modeling-ligand design iterative sequence is utilized to optimize the ligand/receptor interaction, either maximizing the response or minimizing the response (in the case where it is desirable to suppress gene expression rather than induce expression).
>
> 2) Addition of a new ligand "variable domain", wherein the pharmacophore and the complementary binding locus remain more or less constant. An additional group, non-essential but potentially detrimental to binding to natural receptors is attached to the core ligand. The size and nature of this group permits variegated modification and functionalization. As before, the mutant receptor library is then queried.
>
> 3) Wholesale removal of a cluster of ligand pharmacophore elements and replacement with a new PE map (akin to the concept of chimerical structures) wherein one retains roughly half of the known pharmacophore, and replaces the missing pharmacophore cluster with diverse entities. These new molecular fragments provide alternative PE patterns or else partially (but not entirely) replicate the original pattern. Mutant receptor libraries, members of which bear residue modifications at PE binding loci and/or cavity shape modification, are subsequently queried for complementarity to the newly perturbed pharmacophore."

Additional instruction for ligands and receptors is also provided on page 40, line 16 to page 41, line 2, and page 41, line 28 to page 49, line 31.

Further, *Falkner* makes clear that examples are not necessary to support the adequacy of a written description. *Falkner* quoting *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.*:

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification *do not contain examples explicitly covering the full scope of the claim language* (emphasis added by Applicants). That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

As detailed above the written description requirement is satisfied as Applicants' specification provides extensive written description for orthogonal, multiple (i.e. more than one) inducible gene expression systems. For these reasons, Applicants respectfully request that the rejection based on 35 U.S.C. § 112 first paragraph be withdrawn.

Summary

In view of the foregoing remarks and amendments, Applicants submit that this application is in condition for allowance. Therefore, Applicants respectfully request reconsideration and withdrawal of all of the above rejections. If necessary to further prosecution of this application, Applicants welcome further discussion with the Examiner through a formal telephone or in-person interview.

Respectfully submitted,

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